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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/058,546	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003 and 13 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-16,18-21,23-27,29-33,36-59,61 and 63* is/are pending in the application.

4a) Of the above claim(s) *1-7,9-12,18,24,25,29,30,33-38,44,49,54 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,19-21,23,26,27,31,32,39-43,45-48,50-53,56-59,61 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 8, 22, 28, 34, 35, 60, 62 and 64 have been cancelled. Claims 1-7, 9-16, 18-21, 23-27, 29-33, 36-59, 61 and 63 remain pending. Claims 1-7, 9-12, 18, 24, 25, 29, 30, 33-38, 44, 49, 54 and 55 remain withdrawn. Claims 13-16, 19-21, 23, 26-27, 31, 32, 39-43, 45-48, 50-53 and 56-59, 61 and 63 are under consideration in the instant office action.

Applicant's arguments filed 9-8-03 have been fully considered but they are not persuasive. Support for the amendments filed 9-8-03 was provided by applicants on 1-14-04 after a non-responsive letter was sent by the patent office. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The application on pg 12, lines 26-27, is incorrect. It should be WO 9607748.

Information Disclosure Statement

A transmittal sheet for a 2nd supplemental IDS was filed 9-8-3 but no PTO-1449 can be found. Please resend the PTO-1449 so the references can be considered.

Claim Objections

Claims 1-4, 9-12, 33, 36-38 are mislabeled in the response filed 9-8-03 and should be labeled "Withdrawn."

The term "harbouring" throughout the claims should be –comprising--.

Claims 15, 41, 46, 51, 56 should be clarified. The preamble and the phrase "said capsule comprising a porous capsule wall being permeable to the retroviral particles produced by said producer cell" are unclear. The claims should be directed toward a – capsule comprising i) an isolated producer cell line... ...; and ii) a porous capsule wall that is permeable to retroviral particles produced by said isolated producer cell line--.

Claim 63 should be clarified. The capsule implanted should comprise a) packaging cells comprising i) a retroviral vector comprising a DNA sequence encoding SDI-1...; and ii) at least one DNA construct encoding proteins required for said retroviral vector to be packaged; and b) a capsule wall that is permeable to retroviral particles produced by the packaging cells. The claim should be directed toward a method of treating a patient having a tumor or restenosis.

Election/Restriction

This application contains claims 1-7, 9-12, 18, 24, 25, 29, 30, 33-38, 44, 49, 54 and 55 drawn to an invention nonelected with traverse in Paper No. 17. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP ' 821.01. Applicants argue the claims do not encompass antisense because the claims require making viral particles having RNA encoding SDI-1, etc. Applicants argue antisense cannot encode SDI-1, assumably because antisense in the "non-coding strand" used for mRNA synthesis. Applicants'

argument is not persuasive. Claims 5-7, 18, 24 explicitly require the DNA have antisense. Claim 5 is dependent upon claim 1 but is not limited to a viral particle having RNA encoding SDI-1; claim 5 is directed toward the DNA vector used to make the retroviral particle having "antisense to the SDI-1 gene". Claim 1 does not require the vector of claim 5. Applicants' argument is in error because a non-coding strand of the SDI-1 gene does encode SDI-1 because it serves as the template for mRNA synthesis and protein production. Therefore, the restriction is maintained. Claims 1-4, 9-12, 33, 36-38 are mislabeled in the response filed 9-8-03 and should be labeled "Withdrawn."

Claim Rejections - 35 USC ' 112

I. Claims 15, 16, 20, 21, 23, 27, 31, 32, 41, 42, 46, 47, 51, 52, 56-59, 61 and 63 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating restenosis or cancer by contacting the site of restenosis or cancer with a retrovirus encoding SDI-1 resulting in a therapeutic effect, does not reasonably provide enablement for using any mode of delivery as broadly claimed, using producer cells or capsules to treat disease, or using analogues or fragments of SDI-1 to treat disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 21, 26, 27, 32, 59 and 63 are directed toward treating disease using a retrovirus, a producer cell that makes a retrovirus or an encapsulated producer cell that makes a retrovirus encoding SDI-1. The claims are not limited to any route of administration and, therefore, encompass any route of administration. Claim 31 is limited to injecting a retroviral particle "at the site of the tumor" but is not limited to treating patients having tumors (see 112/2nd).

The specification does not enable treating disease, specifically restenosis or cancer, using any route of administration as broadly claimed. Crystal (1995, Science, Vol. 270, page 404-410; page 409) and Feldman (1995, Fundamental & Clin. Pharm., Vol. 9, pages 8-16), both of record, taught the combination of vector and mode of delivery for gene therapy required to target the desired tissue and provide adequate expression of a protein such that a desired effect was obtained was unpredictable. The specification taught administering a retrovirus encoding SDI-1 to tumor cells *in vitro* inhibited hyperproliferation (pg 27, lines 1-7).

Since the time of filing, Nabel (US Patent 5,863,904) taught administering an adenovirus encoding SDI-1 to a site of restenosis *in vivo* treated the disease (col. 8, line 10) and to hyperproliferating smooth muscle cells or tumor cell *in vitro* inhibited hyperproliferation (col. 8, lines 1-3; col. 10, col. 22-26). Nabel taught the adenovirus could be replaced with a retrovirus for delivery of SDI-1 (col. 3, line 10; col. 4, line 60). Nabel was not available to the public until Jan. 26, 1999.

The art at the time of filing did not teach how to treat diseases responsive to the antiproliferative activity of SDI-1 using a retrovirus encoding SDI-1 other than by administering the virus directly to the site of disease. The specification does not correlate administering the virus directly to the site of disease with other modes of delivery to enable any mode of delivery as broadly claimed. Given the unpredictability in the art taken with the teachings in the specification and the post filing evidence of Nabel, it would have required one of skill undue experimentation to determine how to deliver a retrovirus encoding SDI-1 to treat disease other than by direct injection to the site of disease.

Claims 15, 16, 20, 21, 23, 41, 42, 46, 47, 51, 52, 56-59, 61 and 63 encompass capsules comprising producer cells, and methods of using capsules or producer cells to treat disease. The only disclosed use for the capsules comprising producer cells are for therapy *in vivo*. Applicants have not pointed to another purpose for the capsule.

The specification does not provide adequate guidance to use producer cells or capsules comprising producer cells to treat disease. The art at the time of filing did not teach how to administer a producer cell or an encapsulated producer cell making a retrovirus to treat disease. The art at the time of filing and the specification do not teach that the producer cells or capsules produce adequate amounts of retrovirus such that a therapeutic effect could be obtained. Therefore, the specification does not provide adequate guidance regarding the site of administration of producer cells or capsules or

the secretion of retrovirus from the producer cells or capsules that correlates to the amount of retrovirus directly injected to the site of disease that is therapeutic. Given the unpredictability in the art taken with the guidance provided in the specification about how to administer producer cells or capsule to treat disease, it would require one of skill undue experimentation to determine how to administer producer cells or capsules to treat disease.

Response:

Applicants state considerable amount of experimentation is permissible if it is merely routine (pg 15, 4th ¶). Applicants have not provided any reasoning as to why the amount of experimentation would have been routine. However, in this case, the amount of experimentation required to obtain a therapeutic effect using capsules comprising packaging cells producing retroviral particles *in vivo* was not routine because such capsules had not been used *in vivo* to treat disease. The absence of guidance in the art and the specification for how to obtain a therapeutic effect using such capsules indicates that such methods were not in any way "routine."

Applicants' argument regarding Crystal cannot be determined (¶ bridging pg 15-16).

Applicants point to Price and Miller (pg 16, lines 4-6). While Price and Miller state retroviruses will be useful in gene therapy, they are discussing the injection of retroviral particles directly into the patient. The rejection is based on using capsules

comprising packaging cells producing retroviral particles. Price and Miller do not teach how to obtain a therapeutic effect using such capsules.

Applicants point to Nabel (pg 16, 1st full ¶). Nabel does not teach how to use capsules as claimed to treat tumors or restenosis in vivo.

Applicants' arguments regarding Price, Miller and Nabel are repeated in the paragraph bridging pg 16-17.

Applicants argue capsules comprising packaging cells producing retroviral particles were known in the art and could be used *in vivo* to treat disease (pg 17, 1st full ¶). Applicants' arguments are not persuasive. Gunzberg (Curr. Opin. Mol. Ther., Oct. 2001 – Exhibit B) was not available at the time of filing and could not be relied upon for enablement. PCT-EP96/02748 (Salter WO 97/01357, Jan. 16, 1997) was not available at the time of filing and could not be relied upon for enablement. It is noted that Salter teaches no more than the instant application and does not teach obtaining a therapeutic effect using the capsules of the invention. Therefore, Salter could not be relied upon for enablement because Salter is not an enabling disclosure.

Claim 15 encompasses a capsule comprising a producer cell transfected with a retroviral vector encoding a functional analogue or fragment of SDI-1. Claims 46, 47, 51 and 52 encompass capsules comprising packaging cell lines that make retroviral particles encoding amino acids 1-71 or 42-58 of human SDI-1. Claim 63 encompasses a method treating disease using a capsule comprising a producer cell transfected with a

retroviral vector encoding a functional analogue or fragment of SDI-1. Claims 15, 46, 47, 51, 52 and 63 remain rejected for reasons of record regarding functional fragments of SDI-1 capable of treating disease.

Applicants reiterate the argument that they have provided fragments of SDI-1 and an assay for determining fragments, i.e. the *in vitro* assay for the number of cells in G_0/G_1. Applicants' arguments are not persuasive for reasons of record because the SDI-1 must inhibit proliferation of tumor cells or smooth muscle cells causing restenosis *in vivo* . The response to applicants arguments are repeated below:

> Applicants have not provided the amount of inhibition required for a fragment *in vitro* that indicates the fragment is capable of treating disease. Applicants have not provided any data indicating any fragment has the same function as full length SDI-1 such an assay. Without such guidance, it would require one of skill undue experimentation to determine any fragment or analogue of SDI-1 capable of treating disease *in vivo*. It would require one of skill undue experimentation to determine whether a retrovirus encoding amino acids 1-71 or 42-58 of human SDI-1 using any route of administration as broadly claimed would have a therapeutic effect. It cannot be determined whether amino acids 1-71 and 42-58 of the SDI-1 protein as described by El-Deiry, Harper or Xiong have the same antiproliferative activity of full length SDI-1. Therefore, applicants' argument is not persuasive.

If fragments of SDI-1 capable of treating disease *in vivo* were known in the art at the time of filing, please point to such fragments.

II. Claims 13-16, 19-21, 23, 26, 27, 31, 32, 39-43, 45-48, 50-53, 59, 61 and 63 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "a 5' LTR region of the structure U3-R-U5" (13, 15, 39, 45, 50) is unclear. A 5' LTR having such a structure cannot be determined. One of skill would not know when the phrase had been met. It cannot be determined how much of the U3, R or U5 region is required to have the structure of a U3, R or U5 region.

The phrase "one or more sequences selected from coding and coding and noncoding sequences" in claims 13, 15, 39, 45 and 50 is indefinite. It cannot be determined what is being excluded or included by this limitation because the only two types of nucleic acid sequences are coding and noncoding sequences.

The phrase "a 3' LTR region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence containing a regulatory element or a promoter, followed by the U5 and R region, characterized in that at least one of the coding sequences is a sequence encoding SDI-1" in claims 13, 15, 39, 45 and 50 is wholly unclear. The structure of what applicants consider a complete or partial deletion of the U3 region cannot be determined. The metes and bounds of sequences encompassed by the phrase "polylinker sequence containing a regulatory element or a promoter" cannot be determined. It cannot be determined if polylinkers

encompass restrictions sites, splice donors, splice acceptors, promoters and polyadenylation signals or if polylinkers are limited to restriction sites. It cannot be determined if a "polylinker sequence containing a regulatory element or a promoter" has a polylinker and a regulatory element/promoter or if the polylinker is the regulatory element/promoter. It is unclear whether "followed by" means in the 5' or 3' direction. The phrase "characterized in that..." does not describe the 3' LTR and is out of place as written.

The phrase "said SDI-1 sequence encoding a polypeptide with SDI-1 activity of inhibiting cell proliferation" lacks antecedent basis in claims 13, 15, 39, 45 and 50.

The phrase "a polypeptide with SDI-1 activity of inhibiting cell proliferation and being under transcriptional control of said regulatory element or promoter" in claims 13, 15, 39, 45 and 50 is unclear. It is unclear whether applicants are attempting to the function of SDI-1 to a particular activity or whether the nucleic acid sequence encoding SDI-1 is under transcriptional control of the regulatory element/promoter. The proper format for such a vector is: a vector comprising "a nucleic acid sequence encoding SDI-1 operably linked to a promoter".

Claim 15 is indefinite because it is unclear if the capsule comprises the isolated producer cell or if it is simply capable of comprising the producer cell. Replace "which encapsulates" with –comprising—to overcome this rejection.

Claims 21, 27, 31, 59 and 63 are indefinite because "the site of the tumor" lacks antecedent basis in parent claims and is unclear:

Claim 21 is directed toward a method of treating a tumor or restenosis by administering to the individual "at the site of the tumor or the restenosis the capsule."

Claim 27 is directed toward a "method for the treatment of a tumor or restenosis comprising administering to a living animal body, including a human, in need thereof a therapeutically effective amount of a retroviral particle...".

Claim 31 limits claim 27 to administering the particle as an injection at the site of the tumor.

Claim 59 requires treating a tumor or restenosis in an individual, comprising administering to the individual the capsule of Claim 56 at the site of the tumor or the restenosis."

Claim 63 is directed toward a "method for the treatment of a tumor or restenosis comprising implanting a capsule... ...into the living animal body, including a human, in need thereof a therapeutically effective amount of a retroviral particle...".

The claims do not require the "individual" or "living animal body" has a tumor or restenosis. According to the specification, the retroviral particles may be administered to prevent tumor formation in a patient. The particles may be administered to patients with cancerous blood cells that do not have a "site" as claimed. according to the specification, treating metastases is part of the invention, but it is unclear if a

metastases "site" is the organ in which they are found or cancerous tissue itself. It is unclear if these embodiments are intended to be in claim as written. Thus, the metes and bounds of the embodiments to be encompassed or excluded from the claims cannot be determined.

In addition, the phrase "at the site of the tumor" is indefinite in claim 31 because it is unclear if applicants are limiting the claim to tumors or if the phrase is intended to limit the means of administration to injection.

It is unclear if "at the site" in claims 21, 27, 31, 59 and 63 is limited to administering the object directly into the tumor or restenosis or if the phrase encompasses any means that cause administration to the site of the tumor restenosis.

The phrase "the living animal body" lacks antecedent basis in claim 63.

While the wording of the methods of claims 21, 27, 31, 59 and 63 may vary, one suggestion as it relates to treating patients with tumors would be: "A method of treating a patient having a tumor comprising administering a retroviral particle directly into the tumor of said patient..." if adequate support is provided in the specification.

The phrase "living animal body, including a human, in need thereof" in claim 27, 31 and 63 is indefinite. It cannot be determined how the term "body" further limits the phrase. In addition, the phrase "living animal" includes humans, so the phrase "including a human" is unnecessary and confusing. The phrase –living animal— is

recommended if the term "body" and the phrase "including a human" do not further limit the claims. A dependent claim in which the animal is a human would further limit the claims.

Claim 32 remains indefinite because the step of "administering a producer cell line according to Claim 13 to the site of tumor or the restenosis" does not clearly set forth to what the cell line is being administered. The phrase "the site of tumor or the restenosis" lacks antecedent basis. It is unclear if the "site" is *in vivo* or *in vitro*.

Claim 63 remains indefinite because the claim is so unclear. The phrase "a capsule" does not have the same scope as "a porous capsule wall". It is unclear how the "core" throughout the claim is meant to limit the claim. While the capsule comprises cells, it is unclear if the "core" is an additional structure in the capsule or if the cells may be the "core." Deletion of the "core" throughout the claim is recommended. While the claim requires the wall is permeable to retroviral particles produced by the packaging cells, the claim never positively sets forth that the producer cells produce retroviral particles because the particles may never be produced. The phrase "implanting a porous capsule that is permeable to retroviral particles comprising packaging cells harbouring..." would start to clarify the claim; however, further clarification would still be required.

Claim Rejections - 35 USC ' 103

III. Claims 13, 14, 19, 26, 27, 31, 32, 39, 40, 45, 48, 50 and 53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (1989, Biotechniques, Vol. 7, pages 980-990) or Price (1987, PNAS, USA, Vol. 84, pages 156-160) in view of Nabel (US Patent 5,863,904, Jan 26, 1999) for reasons of record.

Miller and Price taught stably transfected packaging cells producing retroviral particles (pg 981, col. 1, col. 3 and pg 156, col. 2, line 18, respectively). The vector of Miller or Price has a 5' LTR having a U3-R-U5 as in claim 13. The vector of Miller or Price has a 3' LTR having a completely or partially deleted U3 region replaced by a promoter followed by R and U5 as in claim 13. The packaging cells are suspended in culture media, which is a "carrier" as in claim 19.

Miller and Price did not teach the retroviral particles encoded SDI-1 or treating restenosis using retroviral particles encoding SDI-1. However, Nabel taught retroviral particles encoding SDI-1 and injecting viral particles into a patient to treat restenosis (see abstract; col. 3, line 10; col. 4, line 60; claim 1; col. 3, line 10). The SDI-1 protein of Nabel encodes full length SDI-1; therefore, the retroviral particle of Nabel encodes full length SDI-1 which comprises amino acids 1-71 and 42-58 of SDI-1 as in claims 45 and 50. The limitation of a pharmaceutical composition is an intended use and does not bear patentable weight in considering the art.

Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to make a stably transfected packaging cell that produces retroviral particles as taught by Miller or Price to make retroviral particles encoding SDI-1 as taught by Nabel. One of ordinary skill would have been motivated to make retroviral particles encoding SDI-1 using the methods of Miller or Price because Miller and Price state the retroviral particles can be used *in vivo* (pg 989, last sentence and pg 157, col. 1, 4th ¶, respectively) and because Nabel taught making and using retroviral particles encoding SDI-1 to treat restenosis (col. 3, line 10).

Response:

Again, applicants' discussion of the obviousness rejection in the response filed 9-8-03 on pg 20-21 compares DNA and RNA viruses, and again, the response is unclear. It is unclear why the words in bold-faced type are being emphasized. It is unclear how the difference between DNA and RNA viruses indicates the combined teachings are not enabling or are missing an element of the claim.

Applicants acknowledge that Nabel taught using a retroviral vector, preferably with impaired ability to replicate (col. 3, line 10) and taught adjusting the titer injected when using retrovirus (col. 4, line 60). However, applicants point out the preferred vector of Nabel was an adenoviral vector. Applicants argue Nabel did not teach a retroviral vector was a preferred vector (pg 20, 1st ¶ of response). Applicants'

arguments are not persuasive. The teachings of Nabel are not limited to only the preferred vector of adenovirus.

Applicants repeat the arguments that there would be no motivation to combine Miller or Price with Nabel because one of skill would not expect a stably transfected producer cell line that makes a retroviral genome encoding SDI-1 could be produced (pg 20, 2nd ¶). Applicants' arguments are not persuasive for reasons of record which are repeated below:

> Motivation to combine the references was provided by Nabel who suggested using a retrovirus to deliver DNA encoding SDI-1 (which can only be made using a retroviral packaging cell line).
>
> Nabel taught making adenovirus encoding SDI-1 using producer cell line 293 indicating producer cells expressing SDI-1 are still capable of producing virus (col. 6, lines 21-42; see line 32 which teaches making adenovirus in 293, an adenovirus producer cell line).
>
> Regarding any "reasonable expectation of success", applicants' argument is also not persuasive. The "reasonable expectation of success" argument is based on that fact that SDI-1 was known in the art at the time to inhibit cell proliferation and DNA synthesis. Therefore, transfecting packaging cells with a vector encoding SDI-1 would prevent cell division and the production of "stably transfected" retroviral packaging cells. Nakanishi of record (1995, EMBO, Vol. 14, pg 555-563) taught cells were commonly transfected to produce SDI-1 (also called p21); Nakanishi stably transfected numerous cells with a vector encoding SDI-1 that survived and replicated for at least 72 hours (pg 562, col. 2, "transfection and determination of DNA synthesis inhibitory activity"). The cells maintained protein production and cellular functions. Just because SDI-1 was known to inhibit proliferation or DNA synthesis does not mean one of ordinary skill

would have thought SDI-1 would prevent proliferation and DNA synthesis in packaging cells - especially because Nabel expressly suggested expressing SDI-1 in a retroviral vector which can only be made using a retroviral particle. If Nabel, who was one of ordinary skill in the art at the time the invention was made, suggested using retroviral vectors to express SDI-1, then there was a reasonable expectation of successfully obtaining retroviral particles expressing SDI-1. One of ordinary skill would have recognized that inhibiting proliferation of or DNA synthesis in a packaging cell expressing SDI-1 would not prevent the production of viral particles. It is noted that the transfected producer cells of claim 13 do not require that the cells have normal proliferation or DNA synthesis. Therefore, one of ordinary skill would have had a reasonable expectation of success in obtaining a stably transfected producer cell line that made retroviral particles encoding SDI-1 as claimed.

Applicants argue Nakanishi did not provide an expectation that a stable packaging cell expressing SDI-1 could be obtained (pg 21, 1st ¶). Applicants' argument is not persuasive. Nakanishi is not relied upon for the rejection and does not have to teach packaging cells expressing SDI-1. Nakanishi has been provided merely to rebut applicants' argument that packaging cells expressing SDI-1 would not have been expected. Nakanishi supports the examiner's rejection by teaching what was known by one of ordinary skill in the art at that time of filing: that numerous cells were stably transfected with a vector encoding SDI-1 at the time of filing. Therefore, one of ordinary skill would have stably transfected any cell with a vector encoding SDI-1. Thus, applicants have not established that one of ordinary skill would not been dissuaded from transfecting any cells, including packaging cells, with a vector encoding SDI-1. The

cells expressing SDI-1 of Nakanishi correlate to packaging cells because they have the same basic cellular structure.

Applicants argue the combined teachings of Miller or Price in view of Nabel did not teach the ProCon vector. Applicants' argument is not persuasive because the vector of Miller or Price has all the limitations claimed. Applicants have not pointed to any specific limitation that is not taught by Miller or Price.

IV. Claims 13, 14, 19, 26, 27, 31, 32, 39, 40, 45, 48, 50 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gunzburg (WO 9607748, March 14, 1996) in view of Nabel (US Patent 5,863,904, Jan 26, 1999).

Gunzburg taught stably transfected packaging cells producing retroviral particles having the structure described in claim 13 (pg 15; Fig. 3; claims 1-5). The packaging cells were inherently suspended in culture media, which is a "carrier" as in claim 19. Gunzburg did not teach the retroviral particles encoded SDI-1 or treating restenosis using retroviral particles encoding SDI-1. However, Nabel taught retroviral particles encoding SDI-1 and injecting viral particles into a patient to treat restenosis (see abstract; col. 3, line 10; col. 4, line 60; claim 1; col. 3, line 10). The SDI-1 protein of Nabel encodes full length SDI-1; therefore, the retroviral particle of Nabel encodes full length SDI-1 which comprises amino acids 1-71 and 42-58 of SDI-1 as in claims 45 and 50.

Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to make a stably transfected packaging cell that produces retroviral particles as taught by Gunzburg to make retroviral particles encoding SDI-1 as taught by Nabel. One of ordinary skill would have been motivated to use the retroviral particles of Gunzburg to deliver SDI-1 as taught by Nabel because the retrovirus of Gunzburg had the advantage of being non-self-inactivating (¶ bridging pg 4-5) and had increased safety (pg 5, 2nd ¶). One of ordinary skill in the art at the time the invention was made would have been motivated to use the retroviral vector of Gunzburg for injecting into a patient because Gunzburg suggested using the viral particles to treat patients (pg 8, 4th ¶; pg 15, last 8 lines).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER